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Chapter 2: Osteoarthritis

INTRODUCTION

- *Osteoarthritis* (OA) is a common progressive disorder of weight-bearing diarthrodial joints, marked by cartilage destruction, osteophyte formation, pain, limited motion, deformity, and disability.

CLINICAL PRESENTATION

- Risk factors include advancing age, obesity and metabolic syndrome, sex, genetics, abnormal joint loading from certain occupations or sports, prior joint injury or surgery, and genetic predisposition.
- The main symptom is deep, aching joint pain that worsens with activity and improves with rest.
- Commonly affected joints include the DIP and PIP joints of the hand, the first carpometacarpal joint, knees, hips, cervical and lumbar spine, and the first MTP joint.
- Limitation of motion, stiffness, crepitus, muscle wasting, and deformity may occur, and lower-extremity involvement can cause weakness or instability.
- Morning joint stiffness usually lasts under 30 minutes and improves with movement.
- Warm, red, tender joints suggest inflammatory synovitis.
- Physical examination may show tenderness, crepitus, and joint enlargement. Heberden and Bouchard nodes are bony enlargements of the DIP and PIP joints, respectively.

DIAGNOSIS

- Diagnosis relies on patient history, physical examination, radiologic findings, and limited laboratory testing.
- Early radiographs may appear normal, but as the disease progresses, typical features include joint-space narrowing, osteophytes, subchondral sclerosis, subchondral cysts, and joint surface deformity.
- Erythrocyte sedimentation rate (ESR) may be mildly elevated when inflammation is present, and rheumatoid factor is negative.
- If obtained, synovial fluid shows high viscosity and mild leukocytosis (<2000 white blood cells/mm^3 [2×10^9/L]) with predominantly mononuclear cells.

TREATMENT

- Goals of Treatment: (1) Educate patients, families, and caregivers, reinforcing key points at follow-ups; (2) relieve pain and stiffness; (3) preserve or improve joint mobility; (4) reduce functional impairment; and (5) maintain or enhance quality of life.

NONPHARMACOLOGIC THERAPY

- Educate patients about the disease, prognosis, and treatment options, and encourage dietary counseling, exercise, and weight loss when

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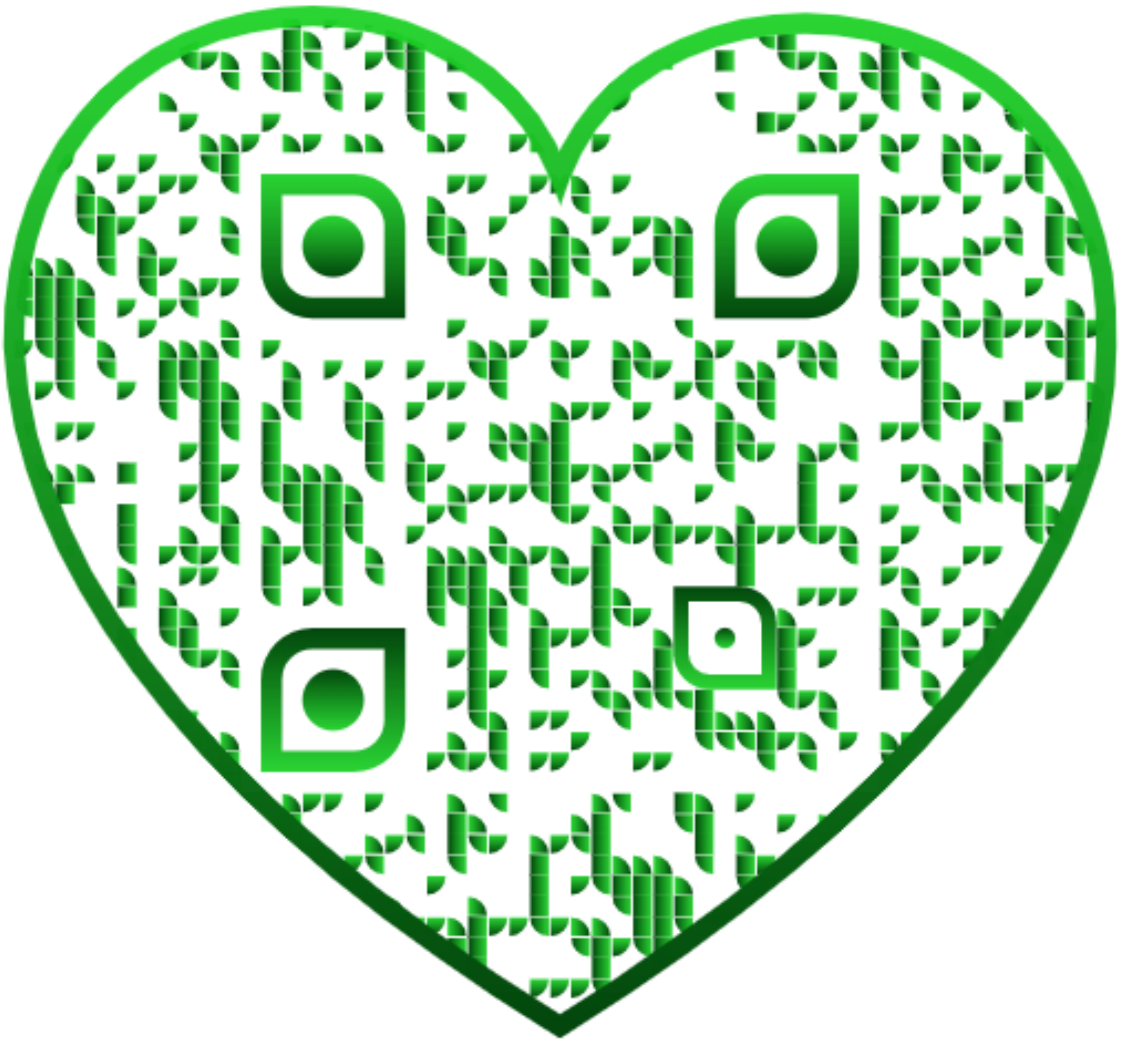

appropriate.

- Physical therapy—using heat or cold and structured exercise—helps maintain range of motion, reduce pain, and lessen reliance on analgesics.
- Assistive or orthotic devices (canes, walkers, braces, heel cups, and insoles) may aid exercise and daily activities.
- Surgical options (eg, osteotomy, arthroplasty, joint fusion) are considered for significant functional impairment or persistent severe pain unresponsive to conservative measures.

PHARMACOLOGIC THERAPY (TABLE 2-1)

TABLE 2-1

Medications for the Treatment of Osteoarthritis

Drug	Starting Dose	Usual Range
Oral Analgesics		
Acetaminophen	325–650 mg every 6 hours or 1000 mg every 6 hours as needed	325–650 mg every 4–6 hours or 1000 mg every 6 hours as needed
Tramadol	25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times daily); thereafter, the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day)	After titration, 50–100 mg can be used as needed for pain relief every 4–6 hours
Tramadol ER	100 mg daily	Titrate to 200–300 mg daily
Hydrocodone/acetaminophen	5 mg every 6 hours based on hydrocodone content	5–10 mg every 4–6 hours as needed
Oxycodone/acetaminophen	2.5 mg/325 mg to 5 mg/325 mg every 6 hours as needed	2.5 mg/325 mg to 10 mg/325 mg every 6 hours as needed for pain
Topical Analgesics		
Capsaicin 0.025% or 0.15%	Test first on a small area of skin; a burning sensation may be experienced	Apply to the affected joint three to four times per day
Diclofenac sodium 1% topical gel	Upper extremity: Apply 2 g to affected joint up to four times daily	ply 2 or 4 g per site as prescribed, four times daily
	Lower extremity: Apply 4 g to affected joint up to four times daily	Apply to not more than two joints at a time
Diclofenac 1.3% topical patch	Apply one patch twice daily to the most painful site	Apply one patch twice daily to the most painful sites
Diclofenac 2% topical solution	Two pump actuations (40 mg) on each painful knee twice daily	Apply 40 mg (two pump actuations) twice daily drops to the affected knee, applying and rubbing in 10 drops at a time; repeat for a total of four times daily
Intra-articular Corticosteroids		

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Triamcinolone acetonide	5–15 mg per large joint (knee, hip, shoulder)	10–40 mg per large joint (knee, hip, shoulder)
Methylprednisolone acetate	4–10 mg for small joints (eg, metacarpophalangeal, interphalangeal); 10–40 mg for medium joints (elbow, wrist); 20–80 mg per large joint (knee, hip, ankle, shoulder)	4–10 mg for small joints (eg, metacarpophalangeal, interphalangeal); 10–40 mg for medium joints (elbow, wrist); 20–80 mg per large joint (knee, hip, ankle, shoulder)
NSAIDs		
Aspirin (plain, buffered, or enteric-coated)	325 mg every 4–6 hours	325–1000 mg every 4–6 hours
Celecoxib	100 mg daily	100 mg twice daily or 200 mg daily
Diclofenac IR	50 mg two or three times a day	50 mg two or three times a day
Diflunisal	250 mg twice a day	250–500 mg twice a day
Etodolac	300 mg twice a day	400–500 mg twice a day
Fenoprofen	400 mg three times a day	400–600 mg three to four times a day
Flurbiprofen	100 mg twice a day	200–300 mg/day in two to four divided doses
Ibuprofen	200–400 mg every 4–6 hours	600–800 mg every 6–8 hours
Indomethacin	25 mg twice a day	Titrate dose by 25–50 mg/day until pain is controlled or maximum dose of 50 mg three times a day
Indomethacin SR	75 mg SR once daily	Can titrate to 75 mg SR twice daily if needed
Ketoprofen	50 mg four times a day	50–75 mg three to four times a day
Meclofenamate	50–100 mg every 4–6 hours	200–400 mg in three to four equally divided doses
Mefenamic acid	500 mg initially, then 250 mg every 6 hours as needed	250 mg every 6 hours as needed
Meloxicam	7.5 mg daily	7.5–15 mg daily
Nabumetone	1000 mg daily as a single dose	500–1000 mg one to two times a day
Naproxen	250 mg twice a day	250–500 mg twice a day
Naproxen sodium	220 mg twice a day	220–550 mg twice a day
Naproxen sodium CR	750–1000 mg once daily	500–1500 mg once daily
Oxaprozin	1200 mg (two 600-mg tablets) once daily	1200 mg (two 600-mg tablets) once daily

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Piroxicam	10 mg daily	20 mg daily
Salsalate	500 mg twice a day	3000 mg daily in divided doses, given two or three times a day

CR, controlled-release; ER, extended-release; IR, immediate-release; SR, sustained-release; XR, extended-release.

General Approach

- Drug therapy targets pain relief, and a conservative approach is appropriate because OA commonly affects older adults with comorbidities.
- Use an individualized, patient-centered strategy and continue nondrug therapies when starting medications.
- Specific drug choices depend on the joints involved, strength of evidence, prior treatment response, patient comorbidities, and concurrent medications.
- In the sections that follow, a s*trong recommendation* is applicable to all or nearly all patients and most would likely want to follow the recommendation; the evidence of efficacy and patient benefit clearly outweigh the risks. A *conditional recommendation* indicates the likelihood that a majority of informed patients would follow the intervention; the quality of evidence is low, or benefit versus risk assessment is close, warranting shared decision making between the healthcare provider and patient.
- **Acetaminophen** is conditionally recommended for hand, knee, and hip OA but is no longer first-line for pain because it offers only minimal benefit over placebo. It is reserved for short-term or intermittent use when NSAIDs are ineffective, not tolerated, or contraindicated.

  ✓ Hepatotoxicity is dose-related; acetaminophen can elevate liver enzymes and cause liver injury even at therapeutic doses. Risk increases with excessive dosing, frequent use, malnutrition, and chronic alcohol intake. The U.S. Food and Drug Administration (FDA) warns of severe liver damage with three or more alcoholic drinks daily and advises patients with chronic liver disease to avoid acetaminophen unless specifically directed.

  ✓ Unintentional overdose is common due to the narrow therapeutic window (max 4 g/day), variable patient sensitivity, widespread availability of combination products, and lack of consumer awareness. CYP2E1 inducers (eg, isoniazid, rifampin, phenobarbital) raise hepatotoxicity risk, and chronic maximal dosing may enhance warfarin's anticoagulant effect, requiring closer monitoring.

  ✓ For short-term or episodic OA pain, acetaminophen should be taken on a scheduled basis, with or without food. Usual dosing is 325–650 mg every 4–6 hours, not exceeding 4 g/day. FDA-recommended OTC limits are lower (immediate-release 325 mg/tablet: 3.25 g/day; extra-strength 500 mg/tablet: 3 g/day). Prescription combination products now contain no more than 325 mg/tablet to reduce overdose risk.
- **Nonselective or COX-2 selective oral NSAIDs** (eg, **celecoxib)** are recommended for knee, hand, and hip OA, with choice guided by individual risk factors. Many experts use oral NSAIDs after acetaminophen failure or when topical therapy is ineffective or unsuitable.

  ✓ Nonselective NSAIDs inhibit both COX-1 and COX-2; COX-1 supports normal physiologic functions such as gastroprotection, while COX-2 is inducible and provides the main therapeutic effect. Thus, COX-2 inhibition yields analgesia and anti-inflammatory benefits, whereas COX-1 inhibition contributes to gastrointestinal (GI), cardiovascular, and renal adverse effects.

  ✓ GI effects are the most common NSAID adverse reactions, ranging from nausea and dyspepsia to serious complications such as perforation, gastric outlet obstruction, and bleeding. Risk factors include prolonged or high-dose NSAID use, multiple NSAIDs, age >60 years, dyspepsia, prior peptic ulcer or bleeding, alcohol use, smoking, and concomitant glucocorticoids or anticoagulants.

  ✓ Strategies to reduce GI risk include: (1) using the lowest effective dose for the shortest duration; (2) adding misoprostol, though diarrhea may limit tolerance; (3) using a daily proton pump inhibitor (PPI) or full-dose H_2 blocker; (4) choosing a COX-2–selective agent (eg, celecoxib); and (5) using topical NSAIDs when appropriate.

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✓ COX-2 inhibitors carry a lower risk of serious GI events compared to nonselective NSAIDs, but this benefit is reduced when patients are also taking aspirin. Importantly, both nonselective and COX-2–selective NSAIDs are linked to an increased risk of cardiovascular (CV) events—including hypertension, stroke, myocardial infarction, and death.

✓ NSAIDs can cause cardiovascular (CV) adverse effects by inhibiting COX-1 and COX-2 enzymes. Both nonselective and selective NSAIDs increase the risk of hypertension, heart failure, stroke, myocardial infarction, and death. Selective COX-2 inhibitors still carry CV risk—but some evidence suggests lower risk compared with higher-dose naproxen or ibuprofen when used at the prescribed dose (eg, celecoxib 100 mg twice daily).

✓ All NSAID labels include warnings of heart attack and stroke risk, which can occur at any time during use; risk increases with higher doses and longer duration, even in people without preexisting cardiovascular disease.

✓ Some NSAIDs interfere with aspirin's antiplatelet effect: ibuprofen ≥400 mg may block aspirin's cardioprotective action if taken before aspirin. To minimize interaction, ibuprofen should be taken at least 30 minutes after aspirin, or aspirin should be taken at least 8 hours after ibuprofen. Other nonselective NSAIDs may also cause such interactions. Acetaminophen does not interfere with the antiplatelet effect of aspirin.

✓ Adverse renal effects of NSAIDs include hypertension, sodium and water retention, acute kidney injury (AKI), interstitial nephritis, papillary necrosis, and worsening of chronic kidney disease. Risk is higher in patients with hypertension, heart failure, diabetes, or volume depletion; these effects are dose- and duration-dependent.

✓ Clinically, NSAID-induced renal problems may present with increased creatinine, hyperkalemia, edema, hypertension, and reduced urine output.

✓ Hepatic toxicity is uncommon but can occur (especially with diclofenac or sulindac), so liver enzymes (AST, ALT) should be monitored and treatment stopped if they rise significantly.

✓ Severe, life-threatening reactions such as Stevens–Johnson syndrome are rare with NSAIDs. Other less common adverse reactions include anaphylaxis (urticaria, angioedema), widespread itching or rash, and CNS symptoms such as dizziness, drowsiness, headache, confusion, depression, and tinnitus. Celecoxib contains a sulfonamide moiety; while its label warns of anaphylactic reactions—and it is contraindicated in patients with aspirin-sensitive asthma—clinical data suggest cross-reactivity with sulfonamide antibiotics is very low. In fact, celecoxib lacks the aromatic amine structure present in sulfonamide antibiotics, which is believed to be responsible for the more severe hypersensitivity reactions.

✓ All nonspecific NSAIDs inhibit COX-1–dependent thromboxane production in platelets, reducing platelet function and increasing bleeding risk. Unlike aspirin, this effect is reversible, with platelet function returning to normal 1–3 days after discontinuation. Celecoxib also reversibly inhibits thromboxane formation.

✓ NSAIDs can interact with lithium (increased levels); warfarin and other anticoagulants/antiplatelet agents (increased bleeding risk); corticosteroids and SSRIs (enhanced bleeding); methotrexate, oral hypoglycemics, ACE inhibitors, ARBs, β-blockers, and diuretics (varied interactions affecting efficacy or toxicity).

✓ NSAID selection should consider prescriber experience, cost, patient preference, prior response, allergies, tolerability, and dosing convenience. Individual responses vary, so if one NSAID is ineffective, switching to another may provide better analgesia.

- **Topical NSAIDs** are strongly recommended for knee OA and conditionally recommended for hand OA. They are not effective for hip OA due to the depth of the joint. Their low systemic absorption makes them a safer initial option than oral NSAIDs, especially for patients ≥75 years or those with comorbidities increasing risk for GI, CV, or renal adverse events.

  ✓ Topical diclofenac provides pain relief comparable to oral NSAIDs for localized OA pain. Onset of relief can occur within hours, with most patients noticing benefit within 1–2 weeks. Topical NSAIDs offer similar analgesia with fewer GI side effects than oral NSAIDs but may cause local reactions such as dry skin, pruritus, or rash.

  ✓ Patients should generally avoid concurrent oral NSAIDs to reduce additive adverse effects. Topical NSAIDs have not been linked to increased cardiovascular risk, though systemic interactions similar to oral diclofenac are possible due to minimal absorption.

  ✓ **Diclofenac 1% gel** (OTC) can be used for hand or knee OA but not the hip or shoulder. Apply 4 g four times daily to the lower limb (eg, foot,

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ankle, knee). Do not exceed 16 g for any single joint. Apply 2 g four times daily to the hand, wrist, or elbow, not exceeding 8 g daily for any single joint. The total daily dose over all joints should not exceed 32 g.

✓ For **diclofenac 2% solution** (knee OA only), use two actuations (40 mg) per knee twice daily, applied via the palm and spread evenly. Patients should avoid contact with the eyes or open wounds and wash hands after application (except when treating hand OA).

✓ The **diclofenac epolamine 180-mg patch** is applied to the most painful area twice daily on clean, dry, intact skin; wash hands after use and avoid contact with the eyes, nose, or mouth.

- **Intra-articular (IA) corticosteroid injections** are strongly recommended as short-term treatments for hip and knee OA when acetaminophen or NSAIDs provide inadequate analgesia or cannot be used. They reduce erythema, swelling, warmth, and tenderness in inflamed joints. Joint aspiration and glucocorticoid injection are performed aseptically, and the aspirate should be examined to exclude crystal-induced arthritis (eg, gout) or infection.

  ✓ **Triamcinolone acetonide** and **methylprednisolone acetate** are preferred because their low solubility prolongs joint residence; typical doses are 40 mg. They offer excellent pain relief, especially when effusion is present. Local anesthetics (eg, **lidocaine, bupivacaine**) are often added for rapid relief, and oral analgesics may be used concurrently.

  ✓ Initial improvement usually occurs within 24–72 hours, with peak relief at 7–10 days and duration of 4–8 weeks. Local adverse effects include infection, osteonecrosis, tendon rupture, and skin atrophy. Therapy is generally limited to three or four injections per year, and injections should not be given more often than every 3 months to minimize systemic effects. Systemic corticosteroids are not recommended in OA due to limited benefit and known long-term risks.

- **Capsaicin cream** is conditionally recommended for knee OA pain in patients who cannot take oral NSAIDs. It is not useful for hip OA because of the depth of the joint. Its use is further limited by modest evidence of efficacy and the risk of accidental transfer to the eyes or other mucous membranes.

  ✓ Adverse effects are mainly local—skin irritation, burning, stinging, and erythema—which usually lessen with continued use. Capsaicin must be applied regularly for benefit, often requiring up to 2 weeks to take effect. Apply four times daily to intact, nonirritated skin. Patients should avoid contact with the eyes or mouth and wash hands thoroughly after application.

- **Tramadol** is conditionally recommended for hand, knee, and hip OA in patients who cannot take oral NSAIDs, are not candidates for intra-articular corticosteroids, or have inadequate response to topical therapies. It may also be used for hip and knee OA when full-dose scheduled acetaminophen and topical NSAIDs have failed. Tramadol can be added to partially effective acetaminophen or oral NSAID therapy.

  ✓ Initial dosing is 25 mg/day, increasing by 25-mg increments every 3 days in divided doses until 100 mg/day (25 mg four times daily) is reached and tolerated. If needed, the dose may be increased by 50 mg every 3 days to 200 mg/day (50 mg four times daily). Once titrated to the lowest effective dose, give 50–100 mg every 4–6 hours, not to exceed 400 mg/day. Tramadol is available alone, combined with acetaminophen, and in extended-release formulations.

  ✓ Adverse effects include opioid-like symptoms—nausea, vomiting, dizziness, constipation, fatigue, headache, sweating, and somnolence—but not the life-threatening GI bleeding, CV events, or renal toxicity seen with NSAIDs. The most serious adverse effect is seizures, which may occur at recommended doses, with concomitant drugs that lower seizure threshold, or in patients with seizure history. Abrupt discontinuation can cause opioid-like withdrawal; tapering is required when stopping therapy. Tramadol is a Schedule IV controlled substance due to its potential for dependence, addiction, abuse, and diversion. There is also increased risk for serotonin syndrome when combined with serotonergic agents, including duloxetine.

- **Opioid analgesics** may be useful for patients who obtain limited pain relief from topical or oral NSAIDs, intra-articular injections, acetaminophen, or who cannot tolerate these treatments. Opioids can effectively relieve acute OA pain for patients with conditions that preclude the use of first-line analgesics. They may also be considered when nonpharmacologic and first-line pharmacologic therapies fail. However, limited long-term efficacy and the risk of adverse effects—including opioid use disorder—limit routine opioid use.

  ✓ When opioid use is appropriate for severe pain, titrate to the lowest effective dose and monitor for efficacy, tolerability, and adverse effects—

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especially constipation, sedation, and dizziness, which increase fall risk. Naloxone should be available for accidental opioid overdose. Patients at high surgical risk who cannot undergo joint arthroplasty may also be candidates. Use the smallest effective dose and quantity, and avoid combining opioids with sedating medications whenever possible.

✓ Inform patients about proper use, storage, and disposal of opioids. Sustained-release formulations may provide more consistent pain control.

✓ Common adverse effects include nausea, somnolence, constipation, itching, dry mouth, urinary retention, bradycardia, peripheral edema, orthostatic hypotension, and dizziness. Respiratory depression can occur with excessive initial dosing, rapid titration, or comorbidities such as sleep apnea or COPD. Long-term therapy may lead to dependence, addiction, tolerance, hyperalgesia, and risks of drug diversion. Assess opioid use at least every three months, reviewing progress toward functional goals, potential harms, and adverse effects.

- **Duloxetine** can be used as adjunctive treatment of knee, hip, and hand OA, particularly in patients with partial response to first-line analgesics such as acetaminophen or oral NSAIDs. Its benefit is mainly as add-on therapy, and pain relief may take up to 4 weeks. Duloxetine may be preferred in patients with both neuropathic and musculoskeletal OA pain.

  ✓ The usual regimen is 30 mg once daily for 1 week, then 60 mg once daily to improve tolerability; a 20-mg dose is available for additional adjustment. Doses above 60 mg increase adverse effects without added benefit.

  ✓ Common adverse effects include nausea, dry mouth, constipation, anorexia, dizziness, fatigue, decreased appetite, hyperhidrosis, and somnolence. Rare but serious events include Stevens–Johnson syndrome and liver failure. GI effects are most common when used for knee OA. Avoid combining duloxetine with medications that increase serotonin (eg, tramadol) due to the risk of serotonin syndrome. When discontinuing duloxetine, taper gradually to prevent withdrawal symptoms such as headache, nausea, diarrhea, irritability, insomnia, and anxiety.

- **Intra-articular hyaluronic acid** (HA) is not routinely recommended for knee pain despite some evidence of moderate analgesic benefit. It is also not recommended for hand OA, and several guidelines strongly advise against its use for hip OA. Limited efficacy, high cost (drug plus administration), and the risk of adverse events limit routine use.

  ✓ Although generally well tolerated, HA injections can cause increased pain, joint swelling, stiffness, effusion, and local skin reactions such as rash, ecchymoses, or pruritus. Serious adverse events, though uncommon, have been reported. HA may be considered when standard therapies are inadequate or when comorbidities limit preferred treatments (eg, NSAID avoidance in patients with GI, cardiovascular, or renal disease). Injections show limited benefit for knee OA and no demonstrated benefit for hip OA. IA preparations and regimens for knee OA include:

  - **Cross-linked hyaluronate 30 mg/3 mL** (Gel-One) single injection
  - **Hyaluronan 30 mg/2 mL** (Orthovisc) once weekly for three injections
  - **Hyaluronan 88 mg/4 mL** (Monovisc) single injection
  - **Hylan G-F 20 16 mg/2 mL** (Synvisc) once weekly for three injections
  - **Hylan G-F 20 48 mg/6 mL** (Synvisc-One) single injection
  - **Sodium hyaluronate 20 mg/2 mL** (Hyalgan) once weekly for five injections
  - **Sodium hyaluronate 20 mg/2 mL** (Euflexxa) once weekly for three injections
  - **Sodium hyaluronate 25 mg/2.5 mL** (Supartz FX) once weekly for five injections
  - **Sodium hyaluronate 25 mg/3 mL** (GenVisc 850) once weekly for five injections

- **Glucosamine** and **chondroitin**: The ACR guidelines conditionally recommend chondroitin for hand OA but strongly advise against its use for knee or hip OA. Glucosamine is strongly discouraged for hand, knee, and hip OA, primarily due to concerns about publication bias.

- Guidelines strongly recommend against use of bisphosphonates, hydroxychloroquine, methotrexate, intra-articular HA for the hip, platelet-rich

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plasma for knee or hip, stem cell injections for knee or hip, and biologics such as TNF-α inhibitors and IL-1 receptor antagonists.

EVALUATION OF THERAPEUTIC OUTCOMES

- To monitor efficacy, assess baseline pain using a visual analog scale and evaluate joint range of motion, including flexion, extension, abduction, and adduction.
- Depending on the joint affected, grip strength and 50-ft walking time can help assess hand and hip/knee OA, respectively.
- Baseline radiographs can document joint involvement and track disease progression.
- Additional measures include the clinician's global assessment of functional limitations, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Stanford Health Assessment Questionnaire, and documentation of analgesic or NSAID use.
- Ask patients about medication adverse effects and monitor for skin rash, headaches, drowsiness, weight gain, or NSAID-related hypertension.
- Obtain baseline labs, including serum creatinine, hematology profile, and liver transaminases, with repeats every 6–12 months to detect toxicities affecting the kidneys, liver, GI tract, or bone marrow.

See Chapter 115, Osteoarthritis, authored by Nancy A. Alvarez and Caitlin K. Cameron, for a more detailed discussion of this topic.

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